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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,765	12/29/2003	Illana Gozes	019856-000210US	8714

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,765	GOZES ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-15,17-22,26-28 and 30* is/are pending in the application.

4a) Of the above claim(s) *2-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-15,17-22,26-28, and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2008 has been entered.

Formal Matters

2. Applicant's Response and Amendments filed 29 October 2008 are acknowledged and entered. Claims 1-8, 10-15, 17-22, and 26-28 are pending. Claims 9, 16, 23-25, and 29 have been cancelled by Applicant. Claims 2-8 are withdrawn, as being drawn to non-elected inventions. New claim 30 has been added. Claims 1, 10-15, 17-22, 26-28 and 30 are under examination. The Declaration of inventor Gozes filed under 37 CFR 1.132 has been considered.

Response to Arguments/Amendments

Claim Objections/Rejections Maintained and New Claim Rejections

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 12, 13, 15, 17-19, and 22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are maintained for reasons of record and for the reasons set forth herein.

Applicant argues that the examiner's reliance on *University of Rochester* and *Ex Parte Kubin* is misplaced and that both cases can be distinguished on their facts (Remarks, p. 7, third paragraph). Applicant argues that unlike the case in *Rochester*, Applicant's have provided an example of a molecule that performs the claimed methods, as SEQ ID NO: 2, the active core site of ADNF III (Remarks, p. 8, last paragraph). Applicant argues that unlike the compounds claimed in *Rochester*, the compounds

recited in the instant claims "comprise a defined structure, SEQ ID NO: 2" (Remarks, p. 9, first paragraph). Applicant argues that unlike *Kubin,* the presently recited eight amino acid ADNF III active core site peptide sequence is invariant (Remarks, p. 9, third paragraph). Applicant argues that that the structural and functional description of the recited compounds used to treat multiple sclerosis are laid out of for those of skill in the art (Remarks, p. 9, third paragraph).

Applicant also argues that the examiner has not followed the recently revised guidelines of the Written Description Training Materials (Remarks, p. 7, third paragraph). Applicant argues that examiner objects to the use of the term "comprising" in claim 1 and that Examples 9 and 10 of the revised Written Description Training Materials are relevant (Remarks, p. 9, fourth and fifth paragraphs to p. 10, first paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

A review of the claim language indicates that the claims are drawn to a method for treating MS comprising administering a composition comprising a genus of ADNF III polypeptides with an active core site of NAVSPSIPQ (SEQ ID NO: 2).

Regarding Applicant's arguments directed to *Rochester* and *Kubin*, the instant claims are in line with the facts and holdings in these cases. The instant claims "comprise" a core sequence of eight amino acid residues (SEQ ID NO: 2). However, the claims are drawn to a genus of polypeptides that can include any one or more amino acid residues on either side of this core sequence. As previously explained of record, the genus of ADNF III polypeptides and the genus of ADNF I polypeptides are highly variable in structure (as shown in the NCBI references recited in the Office Action of 6 July 2006). The structure which is asserted to make up the polypeptide must be clearly and positively specified. The structure must be organized and correlated in such a manner as to present a complete operative embodiment which is adequately described in the specification. The instant disclosure does not provide an adequate description of a sufficient number of structural variants ADNF III and ADNF I polypeptides that function to treat MS. Applicant is referred to the evidence of record showing that the genus of ADNF III and ADNF I polypeptides are highly variable in structure. The general knowledge and level of those of ordinary skill does not supplement the omitted complete structural and functional description because specific, not general, descriptions are needed.

Contrary to Applicant's argument, the examiner does not "object" to the use of the term "comprising." Rather, the examiner merely pointed out that the open language of the word "comprising" in claim 1, for example, places no limit on the number or form of amino acid residues that may be on either side of the core sequence of SEQ ID NO: 2 (NAVPSIPQ) (see p. 3, last paragraph, Office Action mailed 11/27/2007 and p. 3, first paragraph, Office Action mailed 4/29/2008).

Regarding Applicant's arguments directed to the revised guidelines of the Written Description Training Materials, Applicant is reminded that the referenced materials are only guidelines and do not have the force of law. Applicant points to Examples 9 and 10 of the revised Written Description Training Materials. Example 9 is directed to protein variants. Applicant's remarks are directed to Claim 1 of Example 9 (Remarks, p. 9, last paragraph to p. 10, first paragraph). Claim 1 of Example 9 is directed to a complete structural sequence in the form of a composition of matter claim (compare instant claim 10, which is not part of the instant rejection). The instantly rejected claims are very different that claim 1 of Example 9 because the skilled artisan would not know where in the genus of the "treating polypeptides" the core sequence of SEQ ID NO: 2 should be located. For example, would the addition of certain amino acid residues on either side of core sequence stericly interfere with the amino acid residues of SEQ ID NO: 2 (given that they are non-charged with polar hydrophilic residues on either end and non-polar hydrophobic residues in the middle) or their function? Additionally, the examiner has previously explained of record that the polypeptides consisting of SEQ ID NOs: 9, 10, 11, and 12 (of which SEQ ID NOs: 9, 10, 11, and 12 are variants of the core sequence of SEQ ID NO: 2 (NAVSIPQ)) are sufficiently disclosed in the specification because their structure is defined and recited and the amino acid residues of SEQ ID NOs: 9, 10, 11, and 12, that differ from the core sequence of SEQ ID NO: 2 are commonly used linker sequences that are old and well known in the art. However, there are also known inactive ADNF III polypeptides comprising an active core site of SEQ ID NO: 2 that may not be sufficient to support the claimed function of treating MS (see, i.e. SCORE search results 25 April 2006, .rag database, item 41 – WO/200027875, Gozes et al., an 18 amino acid inactive polypeptide comprising SEQ ID NO: 2 at residues 9-18; also recited in the instant specification at paragraph 2). These members of the genus of polypeptides comprising the core sequence of SEQ ID NO: 2 provide evidence that Applicant has not provided sufficient information in the disclosure to establish possession of the full scope of the claimed genus.

Regarding Applicant's argument directed to Example 10, similar to Example 9, the analysis of Example 10 states that claim 1 "provides an actual rejection to practice of a protein comprising SEQ ID NO: 3 and describes **the complete structure** (sequence) of SEQ ID NO: 3" [Emphasis added]. As stated above in reference to Example 9, the instantly rejected claims are very different that claim 1 of Example 9 because the skilled artisan would not know where in the genus of the "treating polypeptides" the core sequence of SEQ ID NO: 2 should be located. Additionally, the examiner has provided evidence of record showing that although there are a few species that are disclosed in the instant specification and known in the art that are active, there are also species in the art that comprise the core sequence and are

inactive (i.e. not functional for the use of treating MS). These known members of the genus of polypeptides comprising the core sequence of SEQ ID NO: 2 with varying functions (or no function at all) provide evidence that Applicant has not provided sufficient information in the disclosure to establish possession of the full scope of the claimed genus.

As previously discussed of record, claim 1, for example, is not limited in the structure that may be encompassed along with the core sequence to effect the function of treating MS. Claims 15 and 22 recite polypeptides of the composition which may encompass up to 44 additional amino acids (about 20 on either side of the recited active core sequence). This translates into a minimum of 4.4×10^{20} possible polypeptide variants, considering only the standard 20 L-amino acids at each position with an unspecified residue. This number increases, when substituting one or more D-amino acids as set forth in claims 12 and 13, 18, and 19. Claims 17-22 are also drawn to the method of claim 1 wherein the composition further comprises a genus of ADNF I polypeptides comprising an active core site comprising SEQ ID NO: 1 (SALLRSIPA), which, in preferred embodiments, may encompass up to 44 additional amino acids. This translates into a minimum of 4.4×10^{20} possible polypeptides, considering only the standard 20 L-amino acids at each position with an unspecified residue. This number would increase if non-standard amino acids or D-amino acids were added, as they are in claims 18 and 19. Even if a polypeptide with an active core sequence of SEQ ID NOs: 1 or 2 would retain the function of the active core sequence, one of skill in the art would still not know anything about the structure of the claimed genus other than the core sequence of 8 or 9 amino acid residues. When viewed in light of the genus of functional polypeptides comprising 44 amino acid residues, the disclosed sequence of 8 or 9 residues only amounts to 18% and 20% of the protein structure, respectively. A genus of polypeptides where only 18% to 20% of the structure is disclosed (meaning that 80% to 82% of the structure is completely unknown) does not have adequate written description. Although the instant claims do not recite a percent identity (such that they would render Example 11 of the Written Description Training Materials relevant) the dependent claims, as set forth above, read on a genus of polypeptides where only 18% to 20% of the structure is known. Given this limited disclosure, the full scope of the claims are not adequately described such that one of ordinary skill in the art would be apprised that Applicant was in possession of the claimed genus.

The examiner has shown of record that the genus of ADNF III polypeptides and the genus of ADNF I polypeptides are highly variable in structure (see NCBI references recited in the Office Action of 6 July 2006). In order to comply with the written description requirement, the structure which is asserted to make up the polypeptide must be clearly and positively specified. The structure must be organized and correlated in such a manner as to present a complete operative embodiment which is adequately described

in the specification. The instant disclosure fails to provide an adequate description of a sufficient number of variant ADNF III and ADNF I polypeptides that function to treat MS. The general knowledge and level of those of ordinary skill does not supplement the omitted description because specific, not general, descriptions are needed.

Applicant has not provided sufficient structural disclosures regarding the claimed genus of core sequence-containing peptides. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 10, 11, 14, 15, 17, 20-22, and 26-28 remain rejected and new claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gozes et al., US Patent 6,613,740 (2 September 2003, priority to 7 February 1997),WO 98/35042 (published 13 August 1998), and Brenneman et al., (US Patent Application Publication US 20020111301, published 15 August 2002) (all previously cited of record), for the reasons of record and the reasons set forth herein.

Applicant argues that the Office Action mistakenly rejects the claims for inherent obviousness (Remarks, p. 10, third paragraph). Applicant also argues that the discovery that ADNF peptides inhibit immune cell proliferation was a surprising result that could not have been predicted at the time of filing of the application (Remarks, p. 10, third paragraph). Applicant argues that the *Schering* and *Toro* cases cited by the examiner ruled on inherency in the context of anticipation, but not an obviousness rejection (Remarks, p. 11, first paragraph). Applicant argues that the Office Action incorrectly applies the standard for inherent anticipation to an obviousness rejection (Remarks, p. 11, first paragraph). Applicant argues that *In re Rjjckaert* is the appropriate standard for inherency in an obviousness rejection (Remarks, p. 11, second paragraph). Applicant argues that the examiner has not made a *prima facie* case of inherency related to obviousness (Remarks, p. 11, second and third paragraphs). Applicant argues that one of skill would have had to recognize the inherent feature at the time of invention or inherent obviousness does not apply (Remarks, p. 11, last paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

The examiner is aware that inherency and obviousness are entirely difference questions. The issue of inherency was not part of the instant rejection in the Office Action mailed 11/27/2007, pp. 6-9. The issue was only raised in response to Applicant's argument (filed 2/26/2008, p. 9, second paragraph) that "the prior art did not appreciate the property of ADNF III polypeptides inhibiting the proliferation of immune cells" (addressed at p. 8 of the Office Action mailed 4/29/2008). The examiner explained that the issue of whether or not the inhibition of the proliferation of immune cells was appreciated by the prior art was not relevant to the instant claims (Office Action of 4/29/2008, p. 9, second paragraph). The instant claims do not require that immune cell proliferation be inhibited. The issue of inherency arose simply because the examiner was trying to explain that this property is a functional physical property of ANDF III polypeptides, regardless of whether or not the property was appreciated. Applicant's instant arguments related to inherent obviousness take the prosecution of the instant claims far afield from the main issue at hand, which is the obviousness of the instantly presented claims over the cited references.

As stated in the Office Actions of record, at the time of the invention, there was a recognized problem or need in the art to treat multiple sclerosis, as evidenced by the cited references themselves. There were a finite number of identified, predictable potential solutions to treat related neurological and autoimmune disorders using an ADNF polypeptide or active core sequence thereof. One of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success because the '740 patent and WO 98/35042 teach the use of ADNF polypeptides for neurological and autoimmune disorders and Brenneman et al., teach the administration of ADNF polypeptides to treat conditions related to increased neuronal cell death. Neuronal cell death is a direct cause of the symptoms of MS. A person of ordinary skill in the art at the time the invention was made would have reasonably known that the ADNF polypeptides would have been useful in the treatment of neurological disorders, including MS. Moreover, WO 98/35042 teaches a list of specific neurodegenerative disorders and also teaches that those of skill in the art will appreciate that the list of neurodegenerative disorders is not exhaustive and that ADNF III polypeptides can be used to treat other neurological disorders (page 8, lines 16-18). The teachings of the prior art, as cited by the examiner, are sufficient to permit a person of ordinary skill in the art to recognize the use of ADNF polypeptides in the treatment of neurodegenerative diseases, including MS. Moreover, the teachings of the prior art provide the rationale and motivations to choose from a finite number of identified, predictable solutions, with a reasonable expectation of success (see MPEP 2141(III) Rationale E, also recited as Examination Guidelines for Determining Obviousness under 35 USC 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*, as set forth of record).

The submission of the declaration of inventor Gozes under 37 CFR 1.132, has been fully considered, but is not persuasive. The declaration states that the cited references do not provide motivation for their combination to arrive at the instantly claimed methods and do not predict that the claimed methods would result for their combination (p. 3, numbered paragraph 6). However, the declarant also admits that "[b]efore the filing date of the [instant] priority application, ADNF III was known to prevent neuronal cell death…" (p. 3, numbered paragraph 7). The statements of the declarant mirror the arguments of Applicant's representative that "it was not known that ADNF III affects non-neuronal cells, including immune cells… (p. 3, numbered paragraph 8), that "[t]he specification provides evidence that ADNF III peptides inhibit proliferation of immune cells using an art accepted animal model of MS, myelin-oligodendrocyte glycoprotein (MOG)-induced chronic experimental autoimmune encephalomyelitis (EAE) in mice" (p. 3, numbered paragraph 9), and that "[p]Post-filing results confirm the ability of ADNF III peptides to decrease levels of tumor necrosis factor-α (TNF-α) and interleukin-12

(IL-12) and also confirm the anti-proliferative effet of ANDF III peptides on T-cells that are activated by a MOG antigen" (p. 4, numbered paragraph 13). Declarant references the Quintana reference to demonstrate the decreased levels of TNFα and IL-12 by immune cells after administration of ADNF III peptides (p. 5, numbered paragraph 14). Declarant states that "[t]he references cited by the Office Action demonstrate that ADNF III peptides prevent neuronal cell death and are silent on ADNF III function related to immune cells" (p. 5, numbered paragraph 15). Although Declarant's statements have been fully considered, they are not persuasive because "treatment of MS" includes treatment by reducing neuronal cell death. Declarant admits that the prior-filed art cited teaches the prevention (reduction) of neuronal cell death by ANDF III polypeptides. Declarant's references to the function of ADNF III on immune cells is not on point with what is presently claimed. Accordingly, the declaration is not persuasive for the purpose of overcoming the instant obviousness rejections of record.

New claim 30 is rejected because the limitations of administration of the peptide to treat MS are taught by the cited references of record. New claim 30 does not add any new method step to the limitations of claim 1 and is merely drawn to the effects of administration. Consequences of administration do not limit the activity of the peptide. Whatever happens after the method step of administration is going to happen as a function of the administration.

9. Claims 12, 13, 18, and 19 remain rejected and new claim 30 is rejected in addition to claims 1, 10, 11, 14, 15, 17, 20-22, and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gozes et al., US Patent 6,613,740 (2 September 2003, priority to 7 February 1997), WO 98/35042 (published 13 August 1998), Brenneman et al., (US Patent Application Publication US 2002/001301 A1, published 15 August 2002), and Voet et al., (1995 Biochemistry, 2nd Ed., p. 67) and Goodman et al., (US Patent 4,587,046, 6 May 1986) (all previously cited of record), for the reasons of record and the reasons set forth herein.

Applicant argues that the Office Action relies on inherency as discussed in the rejection citing Gozes et al., and Brenneman et al., *supra*, as applied to the instant rejection (Remarks, p. 12, first paragraph). Applicant argues that the rejection for inherent obviousness is improper and should be withdrawn (Remarks, p. 12, second paragraph). Applicant's submit Exhibit F, a declaration from inventor Gozes as evidence of the ability of the ADNF III Peptides to "e.g. inhibit immune cell proliferation, is a surprising result" (Remarks, p. 12, third paragraph). Applicant argues that Exhibit F provides evidence that the discovery of the administration of ADNF III peptides inhibit immune cell proliferation and that this is a surprising result (Remarks, p. 13, third paragraph). Applicant also submits post-filing date

references from Quintana et al., (Exhibit H) that demonstrates the ADNF III peptides decrease levels of TNFα and IL-12 secreted by isolated immune cells (Remarks, p. 13, last paragraph to p. 14, first paragraph). Applicant argues that the Gozes declaration provides evidence that the effects of ADNF III on immune cells are independent of the effects of ADNF III on neuronal cells, thus demonstrating that ADNF III affects immune cell proliferation and cytokine secretion that was unexpected and could not have been predicted based on the cited references (Remarks, p. 14, first paragraph). Applicant's arguments and the declaration of inventor Gozes have been fully considered, but they are not persuasive.

In response to Applicant's arguments directed to inherency and obviousness, as stated above, the examiner is aware that inherency and obviousness are entirely difference questions. The issue of inherency was not part of the instant rejection in the Office Action mailed 11/27/2007, pp. 9-11. The issue was only raised in response to Applicant's argument (filed 2/26/2008, p. 9, second paragraph) that "the prior art did not appreciate the property of ADNF III polypeptides inhibiting the proliferation of immune cells" (addressed at p. 10 of the Office Action mailed 4/29/2008). The examiner explained that the issue of whether or not the inhibition of the proliferation of immune cells was appreciated by the prior art was not relevant to the instant claims (Office Action of 4/29/2008, p. 9, second paragraph). The instant claims do not require that immune cell proliferation be inhibited. The issue of inherency arose simply because the examiner was trying to explain that this property is a functional physical property of ANDF III polypeptides, regardless of whether or not the property was appreciated. Applicant's instant arguments related to inherent obviousness take the prosecution of the instant claims far afield from the main issue at hand, which is the obviousness of the instantly presented claims over the cited references.

As stated in the Office Actions of record, at the time of the invention, there was a recognized problem or need in the art to treat multiple sclerosis, as evidenced by the cited references themselves. There were a finite number of identified, predictable potential solutions to treat related neurological and autoimmune disorders using an ADNF polypeptide or active core sequence thereof. One of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success because the '740 patent and WO 98/35042 teach the use of ADNF polypeptides for neurological and autoimmune disorders and Brenneman et al., teach the administration of ADNF polypeptides to treat conditions related to increased neuronal cell death. Neuronal cell death is a direct cause of the symptoms of MS. A person of ordinary skill in the art at the time the invention was made would have reasonably known that the ADNF polypeptides would have been useful in the treatment of neurological disorders, including MS. Moreover, WO 98/35042 teaches a list of specific neurodegenerative disorders and also teaches that those of skill in the art will appreciate that the list of neurodegenerative disorders is not

exhaustive and that ADNF III polypeptides can be used to treat other neurological disorders (page 8, lines 16-18). The teachings of the prior art, as cited by the examiner, are sufficient to permit a person of ordinary skill in the art to recognize the use of ADNF polypeptides in the treatment of neurodegenerative diseases, including MS. Moreover, the teachings of the prior art provide the rationale and motivations to choose from a finite number of identified, predictable solutions, with a reasonable expectation of success (see MPEP 2141(III) Rationale E, also recited as Examination Guidelines for Determining Obviousness under 35 USC 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*, as set forth of record).

As stated above, the submission of the declaration of inventor Gozes under 37 CFR 1.132, has been fully considered, but is not persuasive. The declaration states that the ctied references do not provide motivation for their combination to arrive at the instantly claimed methods and do not predict that the claimed methods would result for their combination (p. 3, numbered paragraph 6). However, the declarant also admits that "[b]efore the filing date of the [instant] priority application, ADNF III was known to prevent neuronal cell death…" (p. 3, numbered paragraph 7). The statements of the declarant mirror the arguments of Applicant's representative that "it was not known that ADNF III affects non-neuronal cells, including immune cells… (p. 3, numbered paragraph 8), that "[t]he specification provides evidence that ADNF III peptides inhibit proliferation of immune cells using an art accpeted animal model of MS, myelin-oligodendrocyte glycoprotein (MOG)-induced chronic experimental autoimmune encephalomyelitis (EAE) in mice" (p. 3, numbered paragraph 9), and that "[p]Post-filing results confirm the ability of ADNF III peptides to decrease levels of tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12) and also confirm the anti-proliferative effet of ANDF III peptides on T-cells that are activated by a MOG antigen" (p. 4, numbered paragraph 13). Declarant references the Quintana reference to demonstrate the decreased levels of TNFα and IL-12 by immune cells after administration of ADNF III peptides (p. 5, numbered paragraph 14). Declarant states that "[t]he references cited by the Office Action demonstrate that ADNF III peptides prevent neuronal cell death and are silent on ADNF III function related to immune cells" (p. 5, numbered paragraph 15). Although Declarant's statements have been fully considered, they are not persuasive because "treatment of MS" includes treatment by reducing neuronal cell death. Declarant admits that the prior-filed art cited teaches the prevention (reduction) of neuronal cell death by ANDF III polypeptides. Declarant's references to the function of ADNF III on immune cells is not on point with what is presently claimed. Accordingly, the declaration is not persuasive for the purpose of overcoming the instant obviousness rejections of record.

As stated above, new claim 30 is rejected because the limitations of administration of the peptide to treat MS are taught by the cited references of record. New claim 30 does not add any new method step to the limitations of claim 1 and is merely drawn to the effects of administration. Consequences of administration do not limit the activity of the peptide. Whatever happens after the method step of administration is going to happen as a function of the administration.

Obviousness-Type Double Patenting Rejection

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 11, 14, 17, 20, and 21 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 21 of now issued US Patent 7,452,867 (previously cited of record as claims 1 and 23 of copending Application No. 11/388,634).

Applicant argues that a two-way test for obviousness is required over the '634 patent (Remarks, p. 14, last paragraph). Applicant argues that the pending application claims priority to a provisional application and a PCT application and the national stage application was filed on 29 December 2003

(Remarks, p. 14, last paragraph). Applicant also argues that the '634 application also claims priority to a provisional application and a PCT application and that the national stage application was filed on 23 March 2006 (Remarks, p. 14, last paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

The '867 patent ('634 application) has a common inventor and a common assignee with the instant application and claims 1 and 21 of the '867 patent are not patentably distinct from instant claims 1, 11, 14, 17, 20, and 21, for the reasons of record and the reasons set forth herein.

Regarding Applicant's argument that a two-way test is required, the reference case is an issued US patent. The effective filing date of the instant application is before the effective filing date of the patent. The first Office Action (a restriction requirement) in the instant case was mailed on 2/28/2006. The first Office Action (a restriction requiremnet) in the '634 application ('867 patent) was mailed on 11/7/2006. Prosecution of the instant application was commenced and advanced prior to the prosecution of the now allowed '867 patent. As such, there was no administrative delay on the part of the USPTO that would cause a delay in the prosecution of the instant application. Accordingly, the one-way test applies. Additionally, Applicant's arguments that the claims could not have been filed in a single application because the claims are directed to the treatment of different diseases (Remarks, p. 15, second paragraph) have been fully considered, but are not persuasive. As stated of record, claims 1 and 23 the '634 application (claims 1 and 21 of the a'867 patent) disclose a method for treating peripheral neurotoxicity in a subject comprising administering a therapeutically effective amount of an ADNF III polypeptide comprising NAVSIPQ (SEQ ID NO: 2) (claim 1 subpart b) (compare instant claims 1, 11, 14) or a mixture of an ADNF III polypeptide comprising NAVSIPQ (SEQ ID NO: 2) and an ADNF I polypeptide comprising SALLRSIPA (SEQ ID NO: 1) (claim1 subpart c) (compare instant claims 1, 17, 20, and 21), wherein said peripheral neurotoxicity is a consequence of treatment with one or more chemical agents; wherein said one or more chemical agent is selected among chemical agents that are used for the treatment of multiple sclerosis (claim 21) (compare instant claim 1). The instant claims and claims 1 and 21 of the '867 patent are drawn to a method of administering a composition comprising an ADNF III polypeptide or an ADNF III and ADNF I polypeptide to treat peripheral neurotoxicity and multiple sclerosis.

The specification of the '867 patent teaches that "[i]In one embodiment, the symptoms of said peripheral neurotoxicity are measured by motor dysfunction, muscle wasting, or a change selected from among a change in sense of smell, vision or hearing, deep tendon reflexes, vibratory sense, cutaneous sensation, gait and balance, muscle strength, orthostatic blood pressure, and chronic or intermittent pain.

In another embodiment, the peripheral neurotoxicity is a consequence of treatment with one or more chemical agents. In another embodiment, the peripheral neurotoxicity is a consequence of treatment with a chemical agent selected from among chemical agents for cancer, multiple sclerosis, gout, arthritis, Bechet's disease, psychiatric disorder, immunosuppression and infectious disease" [Emphasis added] (column 4, lines 1-13; see also claims 1 and 21). Because the claims of the '867 patent encompass treatment of multiple sclerosis, including the specific recitation of a chemical agent used to treat multiple sclerosis in claim 21, Applicant's argument that the instant claims could not have been filed in a single application is not supported by the facts. Accordingly, a one-way test also applies (see MPEP 804).

Applicant is reminded that MPEP § 804 (II) states, "When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure." (Emphasis added). "Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)."

Regarding Applicant's argument that the pending application claims priority to a provisional application and a PCT application, the national stage of which was filed on 29 December 2003. This is factually incorrect. The instant application only claims benefit under 35 USC 119(e) to US provisional application 60/437650, filed 1/2/2003. The instant case is not a national stage entry of a PCT application filed under 35 USC 371. Rather, the instant case is a US application filed under 35 USC 111. It is suggested that Applicant review the Application Data Sheet and the first paragraph of the specification regarding benefit/priority claims. The first paragraph of the specification states that the instant case is "related to" several PCT cases, but there is no claim of priority to any PCT application in the instant case.

As previously stated of record, although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 21 of the '867 patent disclose a method for treating peripheral neurotoxicity in a subject comprising administering a therapeutically effective amount of an ADNF III polypeptide comprising NAVSIPQ (SEQ ID NO: 2) (claim 1 subpart b) (compare instant claims 1, 11, 14) or a mixture of an ADNF III polypeptide comprising NAVSIPQ (SEQ ID NO: 2) and an ADNF I polypeptide comprising SALLRSIPA (SEQ ID NO: 1) (claim1 subpart c) (compare instant claims 1, 17, 20, and 21), wherein said peripheral neurotoxicity is a consequence of treatment with one or

more chemical agents; wherein said one or more chemical agent is selected among chemical agents for multiple sclerosis and immunosuppression (claim 21) (compare instant claim 1). The instant claims are broadly encompass the administration of a composition comprising an ADNF III polypeptide or an ADNF III and ANDN I polypeptide in the treatment of multiple sclerosis. Further, as stated above, the '867 patent teaches that the symptoms of peripheral neurotoxicity are commensurate with the symtoms of MS and that a treatment for peripheral neurotoxicity may be affected by treatment with a chemical agent that treats MS (column 4, lines 1-13; see also claims 1 and 21).

In light of the foregoing, the double patenting rejection is maintained. Applicant is reminded that this rejection is no longer provisional in light of the issuance of the '867 patent.

12. Claims 1, 10, 11, 14, 15, and 26-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 56-59 of copending US Application 11/838,128. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same or overlapping subject matter.

Claims 56-59 of the '128 application recite a method for preventing neuronal cell death and a method for treating a neurodegenerative pathology in a subject comprising administering a therapeutically effective amount of an ADNF III polypeptide comprising the active core sequence NAVSIPQ (SEQ ID NO: 10) (claims 56-59) (compare instant claims 1, 10, 11, 14, 15, and instant SEQ ID NO: 2). Methods of delivery are taught in the specification at p. 65, lines 18-30 (compare instant claims 26-28).

The parameters of the claimed neurodegnerative pathologies are found in the specification of the '128 application. The '128 application teaches that the neurotrophic properties of the ADNF polypeptide have significant therapeutic implications in prevalent neurodegenerative diseases (p. 4, lines 3-10). The use of ADNF III polypeptides to treat numerous forms of neurodegeneration are taught at p. 9, lines 2-16 (see also p. 29, lines 18-33; p. 57, line 18 to p. 59, line 26; p. 63, line 30 to p. 64, line 29; and p. 66, lines 5-11). Instant SEQ ID NO: 2 is taught at p. 12, line 17 as SEQ ID NO: 10. Additionally, the instant specification teaches what is well-known in the art, that although the etiology of MS has not yet been fully elucidated, the major histological hallmarks of MS lesions in the CNS are demyelination with destruction of the myelin sheath and the death of oligodendrocytes, as well as mild to moderate axonal damage and loss, correlating with irreversible neurological impairment (p. 1, paragraph 3). Accordingly, the specification of the '128 application and the general background of the instant application provide evidence of the overlaping scope of the instant claims and those of the '128 application.

Applicant is reminded that MPEP § 804 (II) states, "When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure." (Emphasis added). "Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)."

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Specification - Objection

13. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Methods of Treating Multiple Sclerosis

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:30am-6:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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